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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/021,698	KEITH ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2005 and 27 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 July 2002 and 28 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 2,4,5,7,9,11,15,16,18,19,31,34,35,42,46,56-59,112,114,115,118,120,121,124 and 125.

Continuation of Disposition of Claims: Claims rejected are 2,4,5,7,9,11,15,16,18,19,31,34,35,42,46,56-59,112,114,115,118,120,121,124 and 125.

DETAILED ACTION

This Non-Final Office Action is a reply to the Papers filed 28 January 2005 and 27 April 2005 in response to the Non-Final Office Action mailed 28 July 2004. Claims 1-20, 31-36, 41-43, 46-59, 96-98 and 112-125 were considered in the 28 July Office Action. Claims 1, 3, 6, 8, 10, 12-14, 17, 20, 32, 33, 36, 41, 43, 47-55, 96-98, 113, 116, 117, 119, 122 and 123 were canceled and claims 2, 4, 5, 9, 11, 18, 19, 42, 120, 121, 124 and 125 were amended in the 27 April Paper. Claims 2, 4, 5, 7, 9, 11, 15, 16, 18, 19, 31, 34, 35, 42, 46, 56-59, 112, 114, 115, 118, 120, 121, 124 and 125 are pending and under consideration.

Response to Amendment and Arguments

Rejection of claims 1, 3, 6, 8, 10, 12-14, 17, 20, 32, 33, 36, 41, 43, 47-55, 96-98, 113, 116, 117, 119, 122 and 123 is rendered moot by the cancellation thereof.

Priority

Applicant's perfection of the priority claim to application US 09/881,797 and provisional application 60/211,749 is acknowledged.

Oath/Declaration

Objection to the Declaration is withdrawn in view of the filing of a new Declaration.

Drawings

Objection to the drawings because the margins of Figures 2I, 2K, 2L, 2O, 5B, 5D, 5E, 5F and 5G were insufficient is withdrawn in view of the replacement drawings filed 28 January 2005.

Specification

Objection to the disclosure as containing an embedded hyperlink is withdrawn in view of the amendments thereto.

Claim Objections

Objection to claims 5, 7, 9, 11, 15, 16, 18, 19, 31, 35, 56, 58, 115, 118, 120, 121, 124 and 125 as encompassing nonelected subject matter is withdrawn in view of the amendments thereto.

Claim Rejections - 35 USC § 112, first paragraph

Claims 2, 4, 5, 7, 9, 11, 15, 16, 18, 19, 56, 57, 114, 115, 120, 121, 124 and 125 **stand rejected** under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid comprising the nucleic acid set forth as SEQ ID NO: 19 with the exception that the nucleotide sequence contains a single nucleotide polymorphism of guanine to adenine at position 21 of SEQ ID NO: 5969 or encoding a polypeptide comprising SEQ ID NO: 111 with the exception of an arginine to histidine substitution at amino acid 270, and vectors and isolated host cells comprising said nucleic acid, does not reasonably provide enablement for the broad scope of the nucleic acids encompassed by the claims. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The *prima facie* case was set forth in the 28 July Office Action and is reiterated herein.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The instant claims embrace nucleic acids of tremendous breadth and structural diversity. Independent claims 1 and 2 are directed to a nucleic acid variant encoding a polypeptide, wherein the polypeptide is limited to containing at least one amino acid change which results from the SNP 5969*. Given the broadest reasonable interpretation of this limitation and the absence of any statement of function in the claims, the claimed nucleic acid is limited only to encoding histidine. Although, the claim recites that the nucleic acid encodes the polypeptide sequence set forth as SEQ ID NO: 111, the claim also recites that there is "at least one amino acid change", which would encompass infinite additional changes.

Similarly, independent claims 5, 6 and 41, which are directed to a nucleic acid comprising SEQ ID NO: 19 containing "at least one" SNP as set forth in 5969*, broadly encompasses any nucleic acid comprising an adenine and infinite additional SNP's.

Independent claim 43 is directed to a nucleic acid comprising 15 contiguous nucleotides of a sequence set forth in SEQ ID NO: 19 which contains "at least one" SNP selected from 5969*, and thus encompasses a fragment of any variant of SEQ ID NO: 19.

The dependent claims are directed to fragments and complementary sequences of the nucleic acids claimed in the independent claims, as well as vectors and host cells comprising the nucleic acids.

State of the prior art and level of predictability in the art: It is generally understood in the art that nucleic acids comprising distinct sequences have distinct functional properties and enablement for one nucleic acid sequence encoding histidine or comprising adenine does not provide enablement for all sequences encoding histidine or comprising adenine. Furthermore, although the instant specification demonstrates that some SNP's present in the P2X7 gene are linked to asthma, the art teaches that linkage of individual polymorphisms within a given gene to a given phenotype must be assessed individually. For example, Blumfeld *et al.* (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While, Blumfeld *et al.* were able to demonstrate that some of these polymorphisms are associated with patients having asthma, others are not (see Figure 3). For instance, the marker 10-35/390 was demonstrated to be associated with asthma with a p value of 0.00229, while the marker 10-33/327 was determined not to have a statistical association with asthma (p=0.294). It is noted that the data presented in the instant Table 10 demonstrates a similar phenomenon for the P2X7 gene. For example, Table

12A indicates that SNP's such as 454 H 2 and 454 M 2 are not associated with asthma. Thus, the association of a given SNP with a given disease is highly unpredictable even for SNP's within the same gene.

Amount of direction provided by the inventor and existence of working examples: The teachings of the instant specification which are relevant to the elected invention demonstrate that the 5969* mutation in the P2X7 receptor gene is associated with the asthma phenotype (see especially Table 12). The specification further teaches that nucleic acids can be used to diagnose asthma or identify individuals predisposed to developing asthma (discussion beginning on page 73). However, the vast majority of nucleic acids encompassed by the claims would not have sufficient structural similarity to the P2X7 gene comprising the 5969* mutation to be useful as a diagnostic. The specification is silent with regard to how the skilled artisan might use those nucleic acids that encode histidine or comprise adenine but would not function as a diagnostic for the presence of the P2X7 allele comprising the 5969* SNP.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not know how to use those embodiments of the elected invention which do not comprise sufficient structural similarity to the P2X7 allele comprising the 5969* mutation to detect the mutation. As the claims encompass any nucleic acid comprising the broad structural limitations set forth therein and do not require any particular function, the skilled artisan would have to resort to empirical experimentation divine a use for each claimed embodiment that could not be used as contemplated in the specification. Given the tremendous breadth of the claims the amount of experimentation would clearly be undue.

Response to Amendment and Arguments

In response to the *prima facie* case of record, Applicant has amended independent claims 2 and 5 such that they no longer recite "at least one" and contends that the claims are now limited to a nucleic acid comprising only one single polymorphism change from guanine to adenine at position 21 of SEQ ID NO: 5969.

However, the claims recite that the claimed isolated nucleic acid "encodes a polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 111..." or "comprising a nucleotide sequence as set forth in SEQ ID NO: 19..." Because the indefinite article is used in referring to the disclosed sequence, the claims can reasonably be construed as encompassing any nucleotide encoding or comprising any fragment of the disclosed sequences. For example, any two contiguous amino acids appearing in the sequence set forth as SEQ ID NO: 111 would be "an amino acid sequence set forth in SEQ ID NO: 111". Likewise, any two contiguous nucleotides appearing in the sequence set forth as SEQ ID NO: 19 would be "a nucleotide sequence as set forth in SEQ ID NO: 19". Therefore, the claims still encompass a broad genus of nucleic acids that are not enabled by the teachings of the specification. Therefore, the claims stand rejected under 35 USC §112, first paragraph as lacking an enabling disclosure.

Claims 31, 34 and 35 **stand rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The *prima facie* case was set forth in the 28 July Office Action and is reiterated herein.

Nature of the invention and Breadth of the claims: Claims 31-36 are directed to pharmaceutical compositions comprising the claimed nucleic acids. MPEP 2164.01(c) states, "[w]hen a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that use." Thus, enablement for a claimed pharmaceutical requires that the specification teach an enabled pharmaceutical use.

State of the prior art and level of predictability in the art: With regard to the specific therapeutic utility of a nucleic acid comprising the elected SNP, the art does not recognize any link between the P2X7 receptor and any particular disease such that the skilled artisan would know how to administer a pharmaceutical composition comprising the nucleic acid of the claims to achieve a therapeutic outcome. Thus, the skilled artisan is solely dependent upon the teachings in the specification for the manner and process using the claimed pharmaceutical composition, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected use the same.

With regard to general enablement for the pharmaceutical application of nucleic acids, the art teaches that achieving an effective therapeutic outcome was highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them

expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin *et al.* further states in a report to the NIH that, " ... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that, "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin *et al.* (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck *et al.* (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the delivery of exogenous DNA and its processing by target cells require the introduction of new pharmakokinetic paradigms beyond those that describe the conventional medicines in use today". Eck *et al.* teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ

dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck *et al.* bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3).

In an article published at about the time the instant application was filed, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remained unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical hurdles to be overcome in the future**", beginning on page 116 and continued through page 125).

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. In that regard, the art is silent with respect to what diseases the skilled artisan might treat using the claimed invention or how the claimed pharmaceutical compositions should be

applied to achieve a therapeutic outcome. It should be noted, that Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" (page 131, third full paragraph). Thus, absent explicit teachings as to how the specific technical hurdles might be overcome for a specific disease, the skilled artisan must engage in empirical experimentation to overcome the hurdles before the pharmaceutical application of a given nucleic acid is enabled.

Amount of direction provided by the inventor and existence of working examples: In the discussion beginning on page 90 and continued through the first full paragraph on page 93, the specification provides general guidance as to how one might formulate and administer a nucleic acid to a patient. In the discussion beginning in the paragraph bridging pages 96-97, and continued through page 101, the specification also provides general teachings directed to production of constructs for use in gene therapy. However, the teachings provided were routine in the art well before the instant application was filed and do not address the hurdles that the art teaches must be overcome before therapeutic application of nucleic acid pharmaceuticals is enabled.

Beyond these general teachings, the disclosure provides no specific guidance as to how one would use a pharmaceutical composition comprising the nucleic acid of the elected invention. There are no working examples, and there is even no suggestion as to which patient population should be treated using the nucleic acid. The specification discloses that a P2X7 receptor allele comprising a SNP resulting in an arginine to histidine substitution is linked to asthma. However, it is not clear that the mutation itself is the underlying cause of the condition and, even if it were, it is unclear how administering a nucleic acid comprising the mutation

would produce a therapeutic outcome. Thus, given the teachings provided in the specification, the skilled artisan would not know what patient population to treat using the claimed pharmaceutical, even if therapeutic application of nucleic acids was generally enabled.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to used the claimed pharmaceutical compositions without undue experimentation. In spite of the art-recognized unpredictability of nucleic acid based therapy and the absence of any teachings in the art directed to therapeutic application of the claimed nucleic acids, the specification provides only general teachings of established therapeutic principles, which had not proved enabling for gene therapy as of the time of filing, and provides no specific guidance with regard to therapeutic application of the elected nucleic acids. Thus, one of ordinary skill in the art seeking to use the claimed pharmaceutical compositions would not only have to overcome the hurdles that have generally hindered the development of nucleic acid therapeutics, but would also have to determine experimentally what patient population might respond to the therapy. Clearly, the amount of experimentation required would be undue. Therefore, the instant claims to pharmaceutical compositions fail to meet the enablement requirement of 35 U.S.C. §112, first paragraph.

Response to Amendment and Arguments

In response to the *prima facie* case of record, Applicant first contends that the claims are not limited to a recited use and the claimed pharmaceutical composition has uses other than therapy. Applicant cites examples of teachings directed to use of the polynucleotides to assay for

the presence of 12q23-qter genes; to identify chromosomal abnormalities and allelic variants/mutations; for drug screening; to make transgenic animals; *etc.*

These arguments are not deemed persuasive because the Office construes a composition specifically limited to being a "pharmaceutical" as a composition intended for pharmaceutical use. The examples of alternative uses cited by applicant are not therapeutic applications and therefore would not meet the definition of a pharmaceutical use.

Applicant next contends that the teachings of the specification are, in fact, enabling for uses such as gene therapy. Applicant cites teachings at pages 90-93 and 97-107 as providing adequate guidance as to how to use the claimed pharmaceutical compositions. Applicant contends, "[g]iven the guidance and teachings of the instant specification, combined with the knowledge among those skilled in the art, along with the description, examples and results, it is also submitted that the skilled practitioner, following the teachings of the instant specification, could practice the invention and know how to administer cytokines and co-stimulatory molecules at the appropriate levels and combinations, without undue experimentation" (paragraph bridging pages 20-21).

These arguments have been fully considered but are not deemed persuasive. As discussed in the previous Office Action (see *supra*) the specification provides general guidance as to how one might formulate and administer a nucleic acid to a patient and production of constructs for use in gene therapy. However, the teachings provided were routine in the art well before the instant application was filed and do not address the hurdles that the art teaches must be overcome before therapeutic application of nucleic acid pharmaceuticals is enabled.

Beyond these general teachings, the disclosure provides no specific guidance as to how one would use a pharmaceutical composition comprising the nucleic acid of the elected invention. There are no working examples, and there is even no suggestion as to which patient population should be treated using the nucleic acid. The specification discloses that a P2X7 receptor allele comprising a SNP resulting in an arginine to histidine substitution is linked to asthma. However, it is not clear that the mutation itself is the underlying cause of the condition and, even if it were, it is unclear how administering a nucleic acid comprising the mutation would produce a therapeutic outcome. Thus, given the teachings provided in the specification, the skilled artisan would not know what patient population to treat using the claimed pharmaceutical, even if therapeutic application of nucleic acids was generally enabled. The relevance of Applicant's contention that the skilled artisan would know how to administer cytokines and co-stimulatory molecules at the appropriate levels and combinations to enablement of the instant claims is unclear because the claimed pharmaceutical does not comprise a cytokine or co-stimulatory molecule.

Applicant cites *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.* and *In re Wands* and asserts that the law allows a considerable amount of experimentation if it is merely routine or if the specification provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed.

This argument is not persuasive because, with regard to the legal standard for "undue experimentation", *In re Wands* is clear, "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* ...They include (1) the quantity of experimentation necessary, (2) the amount of

direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims" (8 USPQ2d 1400, page 1404). The present arguments appear to be Applicant's opinion of what is routine experimentation and not the legal analysis set forth in *In re Wands*. In contrast, analysis of the instant claims according to the "Forman factors" is clearly set forth in the previous Office Action and herein above. In view of these considerations and the record as a whole, the skilled artisan clearly would conclude that developing the claimed invention such that it can be used as a pharmaceutical would require a degree of experimentation that is well beyond what is considered routine in the art.

Finally, Applicant contends that the art cited in the previous Office action is not relevant to the instant claims because a pharmaceutical composition comprising complementary nucleic acid sequence may be used to block a gene of interest.

These arguments have been fully considered but are not deemed persuasive. First, with regard to claims 34 and 35, the pharmaceutical composition does not comprise an antisense molecule.

Claim 31 is directed to a pharmaceutical composition comprising an isolated nucleotide sequence that is complementary to the nucleic acid of claim 9 and applicant appears to be asserting that this nucleic acid will be used therapeutically to block expression of the endogenous nucleic acid. However, the examiner can find no teachings in the specification specifically directed to treatment of any condition by administering an antisense molecule comprising the nucleic acid of the claims. Furthermore, as stated above, although the specification discloses that

a P2X7 receptor allele comprising a SNP resulting in an arginine to histidine substitution is linked to asthma, it is not clear that the mutation itself is the underlying cause of the condition. Therefore, the assertion that the claimed nucleic acid could be used to treat any condition is no more than the germ of an idea. "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk* A/S (CAFC) 42 USPQ2d 1001, 1005.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC §112, first paragraph, as lacking an enabling disclosure.

Claim Rejections - 35 USC § 112, second paragraph

Rejection of claims 2, 4, 5, 7, 9, 11, 15, 16, 18, 19, 31, 34, 35, 42, 46, 56-59, 112, 114, 115, 118, 120, 121, 124 and 125 under 35 U.S.C. 112, second paragraph, as being indefinite is **withdrawn** in view of the amendments to the claims.

Claim Rejections - 35 USC § 102 and 103

Rejection of claims 2, 4, 5, 7, 9, 11, 15, 16, 18, 19, 42, 46, 56-59 112, 114, 115, 118, 120, 121, 124 and 125 under 35 U.S.C. 102(b) as being anticipated by Buel *et al.* (17 October 2000) U.S. Patent No. 6,133,434 and claims 31, 34 and 35 under 35 U.S.C. 103(a) as being unpatentable over Buel *et al.* in view of Maniatis *et al.* (1983) Appendix A: Biochemical Techniques, *in* Molecular Cloning: a laboratory manual, Cold Spring Harbor Laboratory, pp. 461-462 is **withdrawn** in view of the acknowledgement of Applicant's priority date.

New Grounds

Specification

The amendment filed 28 January 2005 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendment to the first line of the specification includes an incorporation by reference of the 09/881,797 Application into the instant disclosure. For applications filed prior to 21 September 2004, a priority claim under 35 U.S.C. 120 in a continuation or divisional application does not amount to an incorporation by reference of the application(s) to which priority is claimed. As the priority claim submitted in the transmittal letter did not incorporate the disclosure of the '797 application by reference, any information incorporated by reference in the 21 September amendment that is not already present in the instant disclosure as filed constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 34 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is missing essential elements in that it presently depends from a canceled claim. Claim 34 should be amended to recite the critical elements of claim 14.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 2, 4, 5, 7, 9, 11, 15, 16, 18, 19, 42, 46, 56-59, 112, 114, 115, 118, 120, 121, 124 and 125 are rejected under 35 U.S.C. 102(e) as being anticipated by Buel *et al.* (17 October 2000) U.S. Patent No. 6,133,434.

The grounds for this rejection are the same as those set forth in the previous Office Action regarding anticipation of the claims under 35 USC §102(b). In view of the fact that Applicant had properly amended the first line of the specification in page 3 of the transmittal papers, this new ground for rejection was not necessitated by Applicant's action. Therefore, this Office Action is made non-final.

As described in the previous Office Action, Buel *et al.* discloses a nucleic acid (*i.e.*, SEQ ID NO: 19) that encodes a polypeptide that is 99.3% identical to the instant SEQ ID NO:111 and comprises the arginine to histidine substitution. Buel *et al.* also discloses a nucleic acid that is 99.5% identical to SEQ ID NO: 19 from nucleotide 48-1896 including the G>A substitution (see sequences alignments mailed with the 28 July Office Action). The nucleic acid of Buel *et al.* anticipates the nucleic acid claimed in claims 2, 4, 5, 7, 9 and 42.

Buel *et al.* further contemplates complementary nucleic acids according to the limitations of claims 11 and 46 (see especially column 5, lines 61-63), vectors comprising the nucleic acids according to claims 15, 16, 112, 114 and 115 (see especially column 6, first full paragraph) and transformed host cells according to claims 18, 19, 118, 120 and 121 (see especially the second full paragraph in column 6). In column 5, line 44, Buel *et al.* teaches that the nucleic acids disclosed therein can be used as probes, and in the first full paragraph in column 8, Buel *et al.* teaches the use of a P2X7 probe and a chemiluminescence detection reagent to detect hybridization, which anticipates the kits of claims 56-59, 124 and 125.

As Buel *et al.* teaches nucleic acids, vectors, host cells, kits and compositions comprising each of the limitations of the instant claims, the claims are anticipated by Buel *et al.*

Response to arguments

In response to the rejection under 35 USC §102(b) set forth in the previous Office Action, Applicant contends that Buel *et al.* does not anticipate the instant claims because Buel *et al.* does not disclose a sequence that is identical to the instant SEQ ID NO: 111 or SEQ ID NO: 19.

These arguments have been fully considered but are not deemed persuasive because the instant claims are not limited to a nucleic acid encoding the entirety of SEQ ID NO: 111 or comprising the entirety of SEQ ID NO: 19. As discussed herein above, because the indefinite article is used in referring to the disclosed sequence in the base claims, the claims can reasonably be construed as encompassing any nucleotide encoding or comprising any fragment of the disclosed sequences. For example, any two contiguous amino acids appearing in the sequence set forth as SEQ ID NO: 111 would be "an amino acid sequence set forth in SEQ ID NO: 111". Likewise, any two contiguous nucleotides appearing in the sequence set forth as SEQ ID NO: 19 would be "a nucleotide sequence as set forth in SEQ ID NO: 19". It is further noted that claim 4 requires only that the nucleic acid encode 7 contiguous amino acids, claim 7 requires only that the nucleic acid is 90% identical to the nucleic acid of the base claim, and claims 9 and 42 require only that the nucleic acid comprise 15 contiguous nucleotides. Thus, the nucleic acids disclosed in Buel *et al.* need not encode the entirety of SEQ ID NO: 111 or comprise the entirety of SEQ ID NO: 19 to anticipate the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 4, 5, 9, 11, 15, 31, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buel *et al.* (*supra*), as applied to claims 2, 4, 5, 9, 11 and 15 above, in view of Maniatis *et al.* (1983) Appendix A: Biochemical Techniques, *in* Molecular Cloning: a laboratory manual, Cold Spring Harbor Laboratory, pp. 461-462.

The grounds for this rejection are the same as those set forth in the previous Office Action regarding anticipation of the claims under 35 USC §103(a).

Buel *et al.* discloses a nucleic acid (*i.e.*, SEQ ID NO: 19) that encodes a polypeptide that is 99.3% identical to the instant SEQ ID NO:111 and comprises the arginine to histidine substitution. Buel *et al.* also discloses a nucleic acid that is 99.5% identical to SEQ ID NO: 19 from nucleotide 48-1896 including the G>A substitution (*Id.*). Buel *et al.* does not explicitly teach that the nucleic acid should be comprised within a pharmaceutically acceptable excipient as contemplated in the first paragraph on page 90 of the specification.

The specification teaches that suitable excipients include, "water, saline, dextrose, glycerol, ethanol, or the like and combinations thereof. In addition, if desired, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH-buffering agents, which enhance the effectiveness of the active ingredient" (page 90, lines 20-24).

Maniatis *et al.* teaches that, when dissolving a DNA pellet, one should use a buffer (see step 7) and that DNA can be easily dissolved in buffers of low ionic strength such as Tris-EDTA (see especially Note iv on page 462).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to dissolve DNA, such as the probe of Buel *et al.* in a buffer, which meets the limitations of the instant pharmaceutically acceptable excipient. Motivation to dissolve the DNA of Buel *et al.* in a buffer comes from Maniatis *et al.* who teaches that DNA is soluble in buffers. Absent evidence to the contrary, one of ordinary skill in the art would also have a reasonable expectation of success in dissolving DNA in a buffer given the teachings of Maniatis *et al.* indicating that DNA is soluble in a buffer.

Response to arguments

In response to the rejection under 35 USC §102(b) set forth in the previous Office Action, Applicant contends that the claims would not be obvious over Buel *et al.* in view of Maniatis *et al.* because Buel *et al.* fails to teach the claimed nucleic acids and Maniatis *et al.* does not cure the deficiencies of Buel *et al.* As described above, Applicant contends that Buel *et al.* does not disclose a sequence that is identical to the instant SEQ ID NO: 111 or SEQ ID NO: 19.

These arguments have been fully considered but are not deemed persuasive in view of the record as a whole because the instant claims are not limited to a nucleic acid encoding the entirety of SEQ ID NO: 11 or comprising the entirety of SEQ ID NO: 19. As discussed herein above, the claims can reasonably be construed as encompassing any nucleotide encoding or comprising any fragment of the disclosed sequences and it is further noted that claim 4, and claims 15 and 35 as they depend therefrom, require only that the nucleic acid encode 7 contiguous amino acids, and claim 9, and claims 11 and 31 as they depend therefrom, require only that the nucleic acid comprise 15 contiguous nucleotides. Thus, the nucleic acids disclosed in Buel *et al.* need not encode the entirety of SEQ ID NO: 111 or comprise the entirety of SEQ ID NO: 19 to anticipate the claims. Therefore, the claims are obvious over Buel *et al.* in view of Maniatis *et al.* for the reasons of record.

Conclusion

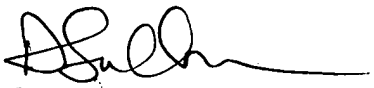
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M Sullivan, Ph.D.
Examiner
Art Unit 1636

DMS



DANIEL M. SULLIVAN
PATENT EXAMINER